

Bringing the physical sciences into your cell biology research

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ABSTRACT Historically, much of biology was studied by physicists and mathematicians. With the advent of modern molecular biology, a wave of researchers became trained in a new scientific discipline filled with the language of genes, mutants, and the central dogma. These new molecular approaches have provided volumes of information on biomolecules and molecular pathways from the cellular to the organismal level. The challenge now is to determine how this seemingly endless list of components works together to promote the healthy function of complex living systems. This effort requires an interdisciplinary approach by investigators from both the biological and the physical sciences.

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INTRODUCTION

The 2012 American Society for Cell Biology Annual Meeting promises to be especially intriguing, with its Meetings-within-the-Meeting themes, which include “Cell Biology and the Physical Sciences.” In our own research, we apply and integrate genetic, biochemical, quantitative imaging, physical, and mathematical approaches in order to understand cytokinesis and cellular mechanosensing (Mohan *et al.*, 2012; Robinson *et al.*, 2012; West-Foyle and Robinson, 2012). In this paper, we explore some of the benefits and challenges of combining disciplines within one’s research. However, it is worth noting that progress in cell biology has always been aided and abetted by the influence of the physical sciences.

For the purposes of this commentary, we define the



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physical sciences as including physics, mathematics, and engineering, and cell biology as representing a similarly broad discipline encompassing genetics, biochemistry, and molecular biology. Biophysics and structural biology naturally straddle both areas.

HISTORICAL PERSPECTIVE: A FEW PIONEERS IN THE FIELD

Researchers in physics and engineering have made significant advances in biology over the centuries. Mendel, who taught physics, laid out the framework for inheritance (Mendel, 1865), which, with the advent of modern molecular biology, gave us the complete genetic information of the cell. In some early optical engineering, van Leeuwenhoek developed a new method to make lenses, which allowed for better visualization of cells (Ford, 2001).

Today, on the basis of his work and the efforts of a large consortium of physicists, mathematicians, and engineers, we have three-dimensional electron microscopy tomography, superresolution imaging, and single-molecule detection and spectroscopy. Before his contribution to the structure of DNA and the central dogma (Watson and Crick, 1953; Crick, 1970), Crick used his training in physics to propel magnetic particles through the cytoplasm, probing its mechanics and structure. He was one of the

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first to describe the cytoplasm as *thixotropic*, that is, having partially elastic behavior (Crick and Hughes, 1950).

Two classic examples in which physical analysis has been central to understanding the function of specific cells are muscle and action potentials in neurons. Muscle research benefited from sensitive calorimetric studies by Fenn and Hill (the latter's undergraduate degree was in physics and mathematics), which revealed the relationship between heat production and work performed by the tissue and led to the force–velocity relationships that define the response of a contractile system to force (Fenn, 1923; Mackey and Santillan, 2005). This framework still guides our thinking on cellular machines. Drawing upon the load sensitivity of muscle, Huxley was then able to discern the broad strokes of how muscle contracts, giving one of the first glimpses into the function of a molecular motor (e.g., Huxley and Simmons, 1971). Eventually, the persistent integration of physical and cell biological methodologies gave rise to single-molecule technologies (e.g., Finer *et al.*, 1994), which allowed for the direct visualization of the workings of molecular motors, and one can now visualize these motor chemomechanics inside living cells. Studies of the function of excitable membranes were steeped in sensitive quantitative assays for measuring ion gradients, detecting currents, measuring membrane potential, and monitoring the opening and closing of ion channels. Huxley and Hodgkin provided critical insight by combining these measurements with mathematical equations and models to allow one to accurately calculate the membrane potentials and predict behavior of these excitable systems (Hodgkin and Huxley, 1952).

A common thread in these examples is that the investigators incorporated concepts from the physical sciences to explore the function and behavior of living systems. While it is tempting to solely emphasize the impact of the physical sciences on cell biology, we should not forget that biology has similarly influenced and motivated new physics—it was scientists' curiosity regarding living systems, such as excitable membrane systems, that led to the development of new analytical tools and an active and important area of applied mathematics and physics (Mackey and Santillan, 2005).

WHAT THE DISCIPLINES BRING TO THE TABLE

Scientific advancements accelerate with team-based approaches. In the integration of physical sciences and cell biology, it is important to note that each set of disciplines contributes essential elements.

The cell biologist typically brings knowledge of biological systems and an intuitive understanding of these systems garnered from years of observing cellular processes. The cell biologist also contributes the logic and tools of genetics, molecular biology, biochemistry, and microscopy. From these approaches come molecular pathways, genetic epistasis, binding interactions and affinities, protein localization and amounts, and an understanding of the dynamics of living systems. Genetic epistasis deserves a special mention, because it provides an important window into the living systems' structure and logic by revealing how the cell uses one set of molecular pathways relative to others. In our case, we started by applying all of these cell biology methods for understanding cytokinesis progression, which provided a set of genetic interactions between key cytoskeletal proteins. We then hypothesized that this framework revealed the biochemical basis for the fundamental physics underlying cytokinetic shape change.

The physical scientist contributes in three major ways. The first is through the development of tools and/or means for measuring biological processes. Recent years have seen a number of physics-based tools, including microfluidics, optical traps, and novel

microscopy techniques that have opened up the study of a number of fields in cell biology. Discoveries in cell biology will continue to benefit from these novel probes, sensors, and imaging methods. We have collaborated with two biophysicists to study the cell's microrheological properties and to measure the force sensitivity and actin-binding lifetime of an actin cross-linker, both of which studies used laser-based optical tracking and trapping methods (e.g., Reichl *et al.*, 2008; Ren *et al.*, 2009). These studies helped open new avenues of research into cytokinesis mechanics.

Because of their inherent variability, biological processes typically require large data sets for proper evaluation. The second major contribution of physical scientists is the extraction of meaningful information from these data sets. Physical scientists are well-trained to analyze quantitative data, employing statistical analyses and other data-mining techniques. Examination of extremely large data sets (with hundreds to thousands of events) can lead to the development of a different perspective on a biological process. We have worked together to develop high content-imaging methods for a variety of cell shape-change processes, such as cytokinesis and chemotaxis (e.g., Xiong *et al.*, 2010).

The final major element physical scientists bring to the table is the ability to assess how the cellular system works in light of physical principles. This part is perhaps the area in which most well-trained cell biologists are typically less comfortable, in large part because they have less formal training in and exposure to these areas. In many cases, this assessment will take the form of a mathematical model. While physical scientists contribute significantly to the mathematics and modeling, cell biologists help provide critical feedback and reality checks to ensure that the theory is biologically grounded. In our group, physical scientists and biologists have persistently pursued the development of physically grounded ideas of how cell shape change works (e.g., Luo *et al.*, 2012; Poirier *et al.*, 2012).

THE IMPORTANCE OF COMMUNICATION IN INTERDISCIPLINARY COLLABORATIONS

By definition, scientists involved in interdisciplinary research come from different fields and professional experiences and have their own biases and points of view. In addition to having different technical skills and areas of expertise, the researchers involved in interdisciplinary research also bring their distinct perspectives and scientific vocabularies, which may be unclear to their collaborators. As examples, *genetic epistasis* and *transfer functions* may not necessarily be familiar terms across the disciplines.

Proper communication of ideas among the scientists is critical for successful collaborations, and scientists need to invest in the collaborative effort, committing to learning each other's perspectives and languages. To help solve this problem, we have made it our practice for many years to hold weekly joint meetings during which all of our trainees present their work in front of one another on a regular basis, which allows everyone to learn to think together. As the principal investigators, we also have weekly lunch meetings to ensure we spend time discussing new results or models. While these interactions are extremely rewarding, this communication aspect is often underappreciated by the scientists flirting with pursuing an interdisciplinary collaboration.

Importantly, the approach toward writing papers and presenting results can also differ significantly between the fields. The manuscript preparation process requires all parties to be very flexible in writing. Often these questions emerge: "Which audience am I writing this for?" and "Is this a physics or a biology paper?" Ideally, we would like our papers to be useful and appropriate for scientists from any discipline, but this is a challenge. We often try a little

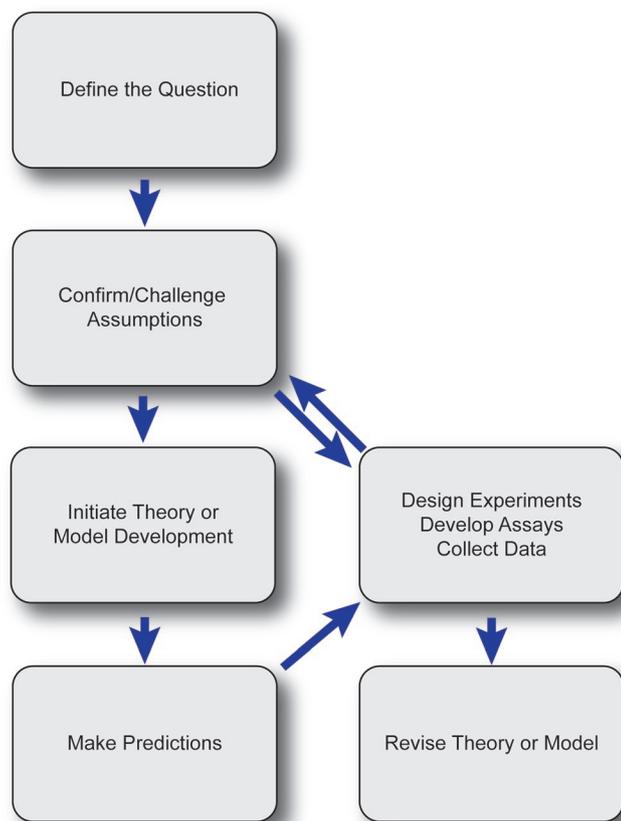


FIGURE 1: Diagram depicts the iterative workflow for developing and testing the physical underpinnings of a cellular process.

“market analysis” to see how understandable our papers are for colleagues from different disciplines.

These differences in paper styles also become particularly apparent when considering a recent analysis showing that mathematical equations presented in the main text of a research paper reduce the numbers of citations for biology papers (Fawcett and Higginson, 2012). If this is true, cell biology researchers could help change this trend.

WORKING BACK FROM THE GOAL, OR AVOIDING THE “HAMMER IN SEARCH OF A NAIL” APPROACH

All fruitful collaborations require the collective agreement on the goal, defining approaches to attain that goal, and importantly, identifying the underlying assumptions (Figure 1). This can be challenging, as fields are sometimes steeped in age-old ideas whose validity may not apply across the board or may violate some physical principles. Simultaneously, it is essential to critically assess what the available data really support. It is advantageous to become very rigorous and strict in the language used to describe any particular set of observations, as this can help close the language gap between the disciplines, helping to ensure that everyone develops a consensus view of what is known and what is not.

With this framework in place, one can begin to develop physical models and theories to explain a biological observation. Typically, models in cell biology begin as cartoon depictions, which are designed to summarize available data and frequently include molecular pathways. However, one ultimately wants to evolve these cartoon depictions into mathematical models

(either analytical or computational) so the model can be tested against physical principles. One ideally wants to develop the model based on a subset of data, reserving other data sets (such as those from a different series of mutants that alter the parameters of the system) to challenge the predictions of the model.

Because diverse systems have different levels of biological complexity and may be better or less well understood, they may require different approaches for analysis and modeling. A poorly characterized system may not be ready for a modeling effort, or may only allow a simpler model that captures a few key aspects of the process. These simple “toy” models can still be quite useful, especially if they are based on measured (or measurable) variables, and the model output can be compared with an experimentally determined parameter. Regardless of the level of complexity appropriate for the model, some of the questions are the same. Are the assumptions right? Is the model physically and biologically grounded?

Models, whatever their form, serve several purposes. Preferably, they help motivate experiments by making testable predictions. However, even if this is not possible, models provide an independent test of our understanding—as simulations based on these models should recreate experimental results, while simultaneously following physical laws. Examples of how these laws manifest themselves in cell biology include the constraints on intracellular transport, the diffusion-based limits on reaction rates, and how forces can deform a viscoelastic network.

MODELS ARE TOOLS: “HOW DO YOU KNOW THERE ISN’T ANOTHER GENE?”

Models, by their nature, are limited to the parameters and assumptions used in their generation. The reality is that with complex living cells, there usually are more elements to the system than can be defined in the model system (at least for now), and the models are therefore incomplete at best and may simply be wrong. By challenging ideas with both models and experiments, one can work iteratively to fill the interpretive holes, which can lead to new experiments, and ultimately discoveries, that would be hard to think of and/or design otherwise. One can also catch errors in models, because model outputs may not fit with some aspect of the biological data or, alternatively, a given model may only be intended to capture certain key aspects of the system. Furthermore, a new model neither automatically renders all prior ones wrong nor is it necessarily an improvement. Models are research tools that expand and test our understanding in much the same way that microscopes and genetic screening strategies help accomplish these same goals.

IMPACT: AN IRREVERSIBLE CHANGE

Overall, integrating the physical sciences with cell biology leads to significant advances for the field. Questions that were unimaginable may now be formulated and posed. The ultimate goal is to achieve predictive power over the system as it functions under diverse conditions and with or without key molecular players. We do leave the reader with one warning: if you choose to bring physical sciences into your cell biology research, you will love it, never choosing to go without it again.

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